Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition

Authors:

Patrick N.A. Harris[1,2*], John F. McNamara[1], David C. Lye[3], Joshua S. Davis[4,5], Louis Bernard[6], Allen C. Cheng[7,8], Yohei Doi[9], Vance G. Fowler Jr[10], Keith S. Kaye[11], Leonard Leibovici[12], Jeffrey Lipman[13,14], Martin J. Llewelyn[15], Silvia Munoz-Price[16], Mical Paul[17], Anton Y. Peleg[18,19], Jesús Rodríguez-Baño[20], Benjamin A. Rogers[19], Harald Seifert[21,22], Visanu Thamlikitkul[23], Guy Thwaites[24,25], Steven Y. C. Tong[4], John Turnidge[26], Riccardo Utili[27], Steven A. R. Webb[28], David L. Paterson[1,29]

1. University of Queensland, UQ Centre for Clinical Research, Brisbane, Australia
2. Department of Microbiology, Pathology Queensland, Central Laboratory, Royal Brisbane & Women's Hospital, Brisbane, Australia
3. Institute of Infectious Disease and Epidemiology, Tan Tock Seng Hospital and Yong Loo Lin School of Medicine, Singapore
4. Global and Tropical Health Division, Menzies School of Health Research, Darwin, Northern Territory, Australia
5. Department of Infectious Diseases, John Hunter Hospital, Newcastle, Australia
6. Infectious Diseases Unit, Tours University Hospital, France
7. Department of Epidemiology and Preventive Medicine, Monash University, Victoria, Australia
8. Department of Infectious Diseases, The Alfred Hospital and Central Clinical School, Monash University, Victoria, Australia

9. Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pennsylvania, USA
10. Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina USA
11. Wayne State University School of Medicine, Detroit Medical Center, Detroit, MI, USA
12. Department of Medicine E, Beilinson Hospital, Rabin Medical Center, Petah-Tiqva; and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
13. Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, QLD, Australia; Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.
14. The University of Witwatersrand, South Africa
15. Division of Medicine, Brighton and Sussex Medical School, UK
16. Froedtert & Medical College of Wisconsin, USA
17. Division of Infectious Diseases, Rambam Health Care Campus and The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
18. Department of Microbiology, Monash University, Victoria, Australia
19. School of Clinical Sciences, Monash Medical Centre, Monash University, Clayton, Victoria, Australia; Monash Infectious Diseases, Monash Health, Clayton, Victoria, Australia
20. Unidad Clínica Intercentros de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospitales Universitarios Virgen Macarena y Virgen del

Rocío - IBiS and Departamento de Medicina, Universidad de Sevilla, Seville, Spain.

21. German Centre for Infection Research (DZIF), Germany
22. Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Cologne, Germany
23. Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
24. Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
25. Nuffield Department of Medicine, University of Oxford, United Kingdom
26. Pathology, Paediatrics and Molecular Biosciences, University of Adelaide, South Australia, Australia
27. Internal Medicine, Second University of Naples, Italy
28. Royal Perth Hospital, and School of Medicine and Pharmacology, University of Western Australia, Perth
29. Wesley Medical Research, Wesley Hospital, Toowong, QLD, Australia

***Corresponding author:**

Dr Patrick Harris

University of Queensland, UQ Centre for Clinical Research, Building 71/918, Royal Brisbane and Women's Hospital, Herston, QLD, 4029, Australia

Mobile: +61 (0) 423785006

Email: p.harris@uq.edu.au

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Abstract

No standardised endpoint definitions exist to aid the design of trials that compare antibiotic therapies for bloodstream infection (BSI). We reviewed endpoints used in contemporary BSI studies and defined consensus endpoints using a modified Delphi process. Prospective studies, randomised trials or registered protocols comparing antibiotic therapies for BSI, published from 2005 to 2016, were reviewed. Different primary and secondary endpoints were defined for pilot (small-scale studies designed to evaluate protocol design, feasibility and implementation) and definitive trials (larger-scale studies designed to test hypotheses and influence clinical practice), as well as for *Staphylococcus aureus* and Gram-negative BSI. For pilot studies of *S. aureus* BSI, a primary outcome of success at day 7 was defined by: survival, resolution of fever, stable/improved Sequential Organ Failure Assessment (SOFA) score and clearance of blood cultures, with no microbiologically-confirmed failure up to 90 days. For definitive *S. aureus* BSI studies, a primary outcome of success at 90 days was defined by survival and no microbiologically-confirmed failure. For pilot studies of Gram-negative BSI, a primary outcome of success at day 7 was defined by: survival, resolution of fever and symptoms related to BSI source, stable or improved SOFA score and negative blood cultures. For definitive Gram-negative BSI studies, a primary outcome of survival at 90 days supported by a secondary outcome of success at day 7 (as previously defined) was agreed. These endpoints provide a framework to aid future trial design. Further work will be required to validate these endpoints with respect to patient-centered clinical outcomes.

Introduction

Bloodstream infection (BSI) is common and potentially lethal. It has been estimated that nosocomial BSI account for 575,000-677,000 episodes and 79,000-94,000 deaths in the USA [1]. It is a frequent reason for consultation with infectious diseases (ID) physicians and clinical microbiologists [2, 3]. The U.S. Food and Drug Administration (FDA) has not approved a new antibiotic specifically for BSI since daptomycin in 2006. However, there is considerable interest among clinicians and pharmaceutical companies in studying different antibiotic choices for this infection.

Defining clinically meaningful endpoints will lend greater credibility and validity to clinical trials on antibiotic treatment. There are no uniform primary endpoints to compare antibiotic options for BSI. Standardised endpoints would have the advantage of facilitating study comparison and reducing data heterogeneity in meta-analyses, as well as providing guidance to researchers when designing studies. The purpose of this article is to describe consensus BSI endpoint definitions for use in future clinical trials and to delineate further work needed in order to optimise these definitions.

Methods

Twenty-seven researchers from 11 different countries working in the field of clinical infectious diseases, microbiology, critical care medicine or biostatistics/trial design agreed to take part in a modified Delphi process [4] in order to develop consensus endpoint definitions for studies comparing antibiotic treatments for BSI. Six rounds of surveys were sent to each participant, with each round building on the results of previous rounds using a web-based survey tool (www.surveymonkey.com). The details of the Delphi process are summarized in Table 1. When unanimous agreement amongst participants was not achieved for any particular question, the level of

agreement and pertinent comments of the participants were then distributed in the next survey round. In this way, consensus was sought. Agreement was defined by majority support (>60% agree) for each component of the definitions.

Literature review

In order to examine pre-defined endpoints currently used by researchers, we reviewed randomised controlled trials and prospective comparative studies assessing antibiotic treatment for adult patients with BSI caused Gram-negative bacilli or *Staphylococcus aureus*. We searched PubMed and Scopus for relevant studies using the terms "prospective", "antibiotic" and "bacteremia" limited to clinical trial article types published between January 2005 and April 2016. We included published trial protocols for actively recruiting BSI studies, by searching ClinicalTrials.gov. We excluded retrospective studies, studies where endpoints were not clearly pre-defined, studies that did not compare antibiotic therapies as a primary aim, those involving fungi or Gram-positive organisms other than *S. aureus*, duplicated studies or those published in languages other than English.

Results

Thirteen different endpoints have been used in contemporary BSI studies. These endpoints are summarized in Table 2 (study details can be found in Supplementary Table 1). The panel agreed that no well validated primary endpoints for the study of antibiotics in the treatment of BSI existed (Round 3: 17 agreed, 0 disagreed). The majority of the panel felt that primary endpoints needed to be different for studies of BSI due to *S. aureus* vs. Gram-negative bacilli (Round 3: 16 agreed, 1 disagreed). This was due to the different spectrum of complications associated with BSI due to

Gram-negative bacilli as compared to *S. aureus*. The majority also felt that endpoints for pilot studies should differ compared to those for large definitive studies (Round 3: 16 agreed, 1 disagreed). The panel agreed that trial endpoints should not be defined by deviation from the trial protocol (Round 4: 18 agreed, 1 disagreed). For example, starting a non-study antibiotic for a secondary infection, or failing to take protocol-defined blood cultures, should not be regarded as clinical failure.

Objective clinical outcomes

The panel agreed that the most objective clinical outcome is mortality, and that it should always be measured as an outcome in trials of antibiotic treatment for BSI. While mortality as an outcome is clearly objective, differences exist as to when mortality should be measured and whether it should be attributed to the BSI as its primary cause.

The panel considered the optimal timing for measuring this outcome. Once this time point is extended far beyond the initial BSI, mortality may become dominated by underlying disease. Mortality has been variably measured 'in hospital' or following discharge, with the timing of mortality determination occurring at 7, 14, 28-30 or 90 days. Early mortality (e.g. 7-14 days) may be more specific for infection-related mortality, but may fail to capture delayed fatalities that could still be influenced by the BSI event. In the consensus definitions, early mortality (7 days) was used for pilot studies, and later mortality (90 days) for larger, definitive studies (Table 3).

Despite the objectivity of mortality as an endpoint, the panel did not agree that mortality should be used as the sole primary outcome measure. Mortality as a sole

outcome may not capture other clinically relevant effects of different antibiotic regimens. The use of attributable mortality was not recommended given the uncertainty of attributing death to the BSI alone (Round 4: 15 agreed 4 disagreed). The panel concluded that mortality should be included as part of any primary endpoint, but should be accompanied by clinically relevant secondary endpoints.

Other objective endpoints such as length of stay in hospital or rates of re-admission were considered by the panel, since they may reflect an important consideration from the point of view of a patient or the "payer" of a healthcare system. In critical care medicine, endpoints such as intensive care unit (ICU)-free days alive have been used [5]. There is likely to be a wide variability in length of hospital stay due to patient or clinician preference or institutional practices. In the absence of uniform standards for discharge from hospital following BSI, these outcomes were not included in the consensus primary endpoints.

Subjective clinical outcomes

Health related quality of life is important to patients. Unfortunately, it is difficult to get a reliable measure of pre-antibiotic quality of life since BSI is an unexpected event, although a measure of "functional status" (e.g. the Karnofsky score [6]) may be more readily determined pre-BSI. The panel concluded that such measures are clearly important for patients, but lack sufficiently robust measurements at the present time to permit their use as primary endpoints, but may be suitable for secondary endpoints. Several panel members suggested that patient-centred measures should be explored in future research and could be adapted from existing scoring systems. Some commonly

used quality of life scores that may be applicable to BSI are summarised (Supplementary Table 2).

Resolution of symptoms relevant to the BSI may be considered evidence of "clinical cure". Even when used in conjunction with resolution of signs of abnormality on physical examination or radiologic investigations, some panel members expressed a view that assessment of "clinical cure" was too subjective to be used as a primary endpoint (although may be considered as a secondary endpoint). However, regulatory authorities such as the FDA or European Medicines Agency (EMA) currently recommend such clinical outcome measures, in conjunction with microbiological response, for registration trials of treatment for urinary tract infection [7, 8]. Given that BSI can represent a heterogeneous clinical entity, especially for Gram-negative organisms, including of a measure of subjective clinical response may be useful in comparing efficacy when the BSI may reflect a final common path for different infectious syndromes (e.g. urinary tract infection, pneumonia, catheter-associated infection). When used, standardised criteria should be employed and assessed by a blinded and independent clinical events committee.

Microbiologic endpoints

A potential microbiologic endpoint is clearance from the blood of the pathogen of interest. This has been used as a primary endpoint in a recent pilot study of antibiotic regimens for methicillin-resistant *S. aureus* (MRSA) BSI [9], and as a secondary endpoint in a trial evaluating continuous infusion of beta-lactam antibiotics [5]. The panel considered that this endpoint is less relevant for Gram-negative BSI, where prolonged bacteraemia is uncommon [10] and much less frequent than for *S. aureus*

[11]. Breakthrough infections may be of relevance for some Gram-negative BSIs, such as AmpC-hyperproducing variants of *Enterobacter cloacae* [12].

The panel agreed that relapse of BSI or recurrence of infection at a distant site was an important endpoint for *S. aureus* BSI. This endpoint should always be used in conjunction with clinical endpoints. Furthermore, recurrence of infection at a distant site may not always be amenable to microbiological confirmation by culture (e.g. vertebral osteomyelitis), and some panel members expressed a view that this may be better defined as a clinical endpoint. However, given the lack of specificity in determining microbiological failure without culture confirmation, the consensus endpoints require culture of *S. aureus* from sterile sites to define failure (Table 3). The optimal duration of follow-up required to capture these events is uncertain. However, the great majority of cases relapse within 6 weeks of initial BSI [13, 14].

An additional area of uncertainty is defining the optimal clinical samples to include in the follow-up period to determine microbiological failure. For BSI studies it may be important to discriminate between persistent and relapsed BSI by including stipulation for collection of 'clearance' blood cultures. A protocol that requires frequent additional blood sampling may also suffer from limited adherence and consequent missing data. Furthermore, relapse of infection at distant sites (e.g. bone and joint infection) would need to be captured by also including sterile site specimens. Inclusion of non-sterile samples (e.g. sputum, urine) would be less specific for true microbiological relapse. Appropriate molecular typing methods should be applied to discriminate between re-infection and relapse.

Surrogate endpoints

Surrogate endpoints have been used extensively in clinical trials within other areas of infectious disease (e.g. HIV viral load [15]). For trials comparing treatment for BSI, investigators could potentially measure response to therapy either by using relevant biomarkers (e.g. C-reactive protein, procalcitonin) or clinical parameters (e.g. an illness severity score).

The panel considered what attributes would constitute a useful surrogate marker in the context of BSI. Practical definitions of a meaningful surrogate marker are available (see Panel 1, supplementary data) [16]. Essentially, a surrogate must capture any relationship between the treatment and the true endpoint of interest. The panel expressed the view that while the use of surrogate outcomes has potential advantages, great care needs to be taken in the selection and validation of the surrogate outcome.

The panel considered the role of measuring resolution of clinical features of infection (e.g. fever, tachycardia, white cell count) as a surrogate endpoint. However, it was agreed that these markers could not be used as a sole primary endpoint, given that so many variables other than antibiotic activity may have an influence. There was interest in using the Sequential Organ Failure Assessment (SOFA) score, which captures information on respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems [17] and can be used to assess daily changes in a patient's status within the ICU. This is an advantage over APACHE [18] or SAPS [19], which predict mortality based on the first 24 hours of observation. However, SOFA requires measurements that are only generally applicable in ICU, such as arterial blood gas analysis. A modified SOFA score may be more applicable to general ward patients

[20]. Other scoring systems of disease severity that may be applicable in BSI studies were discussed and are summarised in Supplementary Table 3.

The consensus panel universally agreed that no reliable or well-validated surrogate endpoint for mortality currently exists to use in BSI trials (Round 3: agreed 17, disagreed 0). They may have greater applicability in phase II trials or be used as part of secondary outcome measures in phase III trials.

Composite endpoints

Composite endpoints can enhance the power of a clinical trial and capture a wider spectrum of clinically relevant events and increase the expected event rate. However, several members of the panel expressed caution. The frequency of combined events may not occur in the same direction cancelling-out an overall effect. Furthermore, one component of the combined outcome may be more clinically important than another, and significant differences may be driven by less serious outcomes. As such, each component of a composite outcome should be reported separately to assess the direction and size of each effect. If more than one primary endpoint is used, the chance of obtaining a significant result by chance alone is also increased. Appropriate weighting of components of greater significance is essential but the panel could not find examples where they were used in trials of BSI.

The panel considered composite endpoints used or proposed in trials of *S. aureus* BSI. The endpoints used in a published randomised controlled trial (RCT) of daptomycin vs. vancomycin for treatment of BSI, which used a primary outcome of clinical success at 42 days (with failure defined by clinical and microbiological factors as well

as protocol violations) [21] came under criticism. Concerns included failure defined by starting a non-study antibiotic for a secondary infection, or failing to take protocol blood cultures. The primary endpoints used by the ARREST [22] (co-primary outcome of all-cause mortality up to 14 days from randomisation and bacteriological failure/all-cause mortality up to 12 weeks) or CAMERA [9] (composite primary endpoint at 90 days of all-cause mortality, persistent bacteraemia at day 5 or beyond, microbiological relapse, or microbiological treatment failure) studies were felt to be more appropriate, although consensus could not be reached as to which endpoint was superior.

New composite endpoints for BSI caused by *S. aureus* and for Gram-negative organisms with a >10% risk of mortality (e.g. *E. coli*) were determined by consensus (Table 3) (Round 5: *S. aureus*, 15 agreed, 3 disagreed; Gram-negatives, 14 agreed, 4 disagreed). Unanimous agreement was not reached on the components of these composite primary endpoints. The advantages and disadvantages of the various primary endpoints discussed by the panel are summarized in Table 4.

Ordinal Scales

The panel considered the use of a desirability of outcome ranking (DOOR) score as described by Evans and colleagues [23]. Our panel was not able to reach consensus on this topic (Table 1) (Round 6: 10 Agree, 9 disagreed). The perceived advantages and disadvantages of a desirability of outcome scale by our panel are summarised in Table 4.

Discussion

BSI is a common condition encountered by ID physicians and clinical microbiologists, yet many questions remain as to its optimal management. In a recent survey, ID physicians were asked to rank proposals for RCTs in terms of which were most likely to change their practice. Five of the ten top-ranking RCT proposals were related to BSI due to *S. aureus*, *Enterococcus* or multiresistant Gram-negative pathogens [3]. Seventeen investigator-initiated RCTs on antibiotic therapy for BSI are currently registered as recruiting patients (clinicaltrials.gov, accessed on 16th April, 2016). Despite this research activity, there is no generally accepted primary endpoint for these studies [24]. Some regulatory guidance for endpoint selection in therapeutic trials is available for certain infectious disease indications from the FDA [8, 25] but they do not directly address BSI studies [24]. The EMA guidelines recommend the use of a clinical outcome (defined as cure, failure or indeterminate) measured at a fixed number of days post randomisation according to pre-determined definitions, with microbiological cure as a co-primary endpoint should this be of equal importance (e.g. in endocarditis) [7, 24]. One key issue identified by the panel was that endpoints required by regulatory authorities may be different from pragmatic investigator-initiated trials where, for instance, established agents or strategies are compared. These differences are summarized in Table 5. The endpoints presented here are not intended to replace guidance from regulatory bodies, where the purpose is to gain approval for a novel drug or therapeutic intervention. We hope that future management of patients with BSI will be guided by research addressing questions routinely faced by clinicians. These studies are likely to be pragmatic, often investigator-initiated, perhaps involving optimisation of existing drugs or treatment strategies, and closely reflecting 'real-world' dilemmas.

One issue that has been previously considered by regulatory agencies is whether BSI should be considered as a separate clinical entity without reference to the likely source of infection.[26] The EMA and FDA have previously suggested that approving an indication for BSI without reference to the underlying cause is problematic, since this may imply efficacy regardless of the primary focus of infection.[26, 27] This may be most important for Gram-negative BSI, which is a heterogeneous condition, reflecting several possible clinical syndromes. For *S. aureus* BSI, 'uncomplicated' infections (such as vascular catheter-associated BSI with prompt line removal and no metastatic focus) represent a different spectrum of disease from endocarditis, vertebral osteomyelitis or primary BSI with unknown focus.

BSI may not always be a useful target for new drug in development seeking a labelled indication, but for pragmatic investigator-initiated studies BSI is a highly relevant entity. BSI is common, is usually clinically unambiguous (at least for *S. aureus* and pathogenic Gram-negative bacilli), is associated with considerable morbidity and mortality and is easily detected in the laboratory. Furthermore, the presence of BSI requires decision-making in response to a clinical entity for which rigorous evidence is frequently lacking. Therefore, we believe that the application of standardised endpoints in the study of BSI is meaningful, even if it may reflect a heterogeneous group of clinical phenomena.

A number of clear differences in opinion amongst the panel were present. A philosophical divide existed between panel members who felt that only patient-centred outcomes (how a person feels, functions or survives) should be used for primary endpoints in large, pragmatic, practice-defining trials. This implies that only

mortality or a measure of disability as a result of the BSI should be used as a primary endpoint. In other words, prolonged bacteraemia or other indicators of microbiologic failure are irrelevant to any given patient. The alternate philosophic viewpoint is that markers of antibiotic activity include microbiologic response, as well as clinical response, and that evidence about this response has an important influence on whether a physician will choose any particular antibiotic regimen.

The recent proposal by Evans and colleagues of the DOOR concept [23] provides a potential methodology to address non-inferiority and integrate patient centred outcomes and mortality along with appropriately validated surrogates. It also has the potential to provide a single scale for both pilot and definitive studies. Given the novel nature of the methodology, it was raised with the panel for discussion. Our panel were divided regarding the utility of this methodology. A commonly raised concern was its complexity, leading to uncertainty in how to interpret results and the potential for introducing bias. When a smaller number of categories are used in a DOOR scale or if most patients fall into a small number of categories, this may increase power, raising the possibility that category definitions could be manipulated to increase the likelihood of demonstrating superiority [28]. A DOOR score requires consensus in terms of the components of the ordinal scale, and it is not yet clear how these should be defined. Endpoints can be ranked in order of importance in their assessment of comparative antibiotic activity. For example, in an assessment of *S. aureus* BSI, mortality may be ranked highest, followed by relapse of infection requiring open surgery, relapse after treatment is completed, slowness in fever settling and delay in clearance of bacteremia. Adverse events could also be incorporated into the rankings. A potential advantage of such an approach is that it is generally

congruent with physician assessment of the consequences of *S. aureus* BSI. Whether this approach is also congruent with a patient's experience remains to be determined.

Future research could address some of these uncertainties by using existing or prospectively collected data. Such studies would require definition of 'true' outcomes, incorporating patient-centred variables (which may benefit from the input of patients themselves) and measures that are often overlooked, such as quality of life assessment. Early surrogate measures of "success" could then be validated against these 'true' outcomes. Given that increased mortality following sepsis can be demonstrated for up to 2 years post event [29] such validation studies may require follow-up beyond the usual 30 or 90 days. Once 'true' outcomes have been established in observational studies, a proposed ordinal scale could be formulated and validated for the use in clinical trials. The optimal time point for determining primary outcomes remains to be determined and further research is warranted to address this uncertainty.

It is also important that studies comparing treatment for BSI ensure that other evidence-based approaches known to influence clinical outcomes (such as seeking and addressing a removal source of infection or ID consultation for *S. aureus* BSI [30]), are applied consistently between arms and compliance recorded.

Limitations of these consensus endpoints are acknowledged. Universal agreement was not achieved for all components of the definitions, and not all participants contributed towards every round. The definitions are largely derived from expert opinion where clinical evidence is sparse. Even for questions where consensus was

achieved, this does not ensure that the chosen approach is without pitfalls. For instance, it was strongly agreed that endpoints should be defined differently between pilot and definitive studies. However, a contrary view might be that endpoints should be consistent between all phases of a clinical trial. This may be of concern when testing multiple early phase drug treatments for efficacy and safety signals, which could lead a significant 'false discovery' rate.[31] When testing multiple hypotheses (especially using a traditional p value criterion of <0.05 for significance), a 'positive' early phase trial may represent a statistical anomaly that fails to translate into a significant effect in later phase trials. It is unlikely that a 'perfect' set of endpoints can be currently defined, but this work can provide a basis for future evidence-based refinement.

In conclusion, we have proposed primary endpoints that could be used in future observational and interventional studies of antibiotics for BSI. It is also hoped that this manuscript will stimulate further research into which endpoints are most likely to enhance antibiotic prescribing practices and improve patient outcomes.

Author contributions

DLP, PH, JMcN conceived the idea for the manuscript and wrote the initial and final drafts. JMcN undertook the literature search. All authors participated in at least one round of the Delphi process and contributed to the preparation of the manuscript. All authors have reviewed and approved the final version of the manuscript.

Transparency Declaration

AC is a member of the Advisory Committee for Prescription Medicines (ACPM), which advises the Australian Therapeutic Goods Administration (TGA) on drug regulation issues. The opinions expressed in this paper may not represent the views of the ACPM or the TGA.YD has served on advisor boards for Shionogi Inc., Meiji, Tetraphase and Achaogen, consulted for Melinta Therapeutics, and received research funding from Merck and the Medicine Company for studies unrelated to this work. VGF served as Chair of the V710 Scientific Advisory Committee (Merck), has received grant support or has grants pending from NIH, MedImmune, Forest/Cerexa, Pfizer, Merck, Advanced Liquid Logics, Theravance, Novartis, Cubist, has been a paid consultant for Pfizer, Novartis, Galderma, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Cubist, Basilea and has received honoraria from Green Cross, Cubist, Cerexa, Durata, Theravance. MJL has been scientific advisor for Roche, Pfizer, Astellas, and InfectoPharm and has been a speaker for Astellas. JRB has been scientific advisor for Achaogen, AstraZeneca, Roche, Pfizer, Merck, Novartis and InfectoPharm, and has been speaker for Pfizer, Novartis, Astellas, AstraZeneca and Merck. HS reports financial relationships with Astellas, AstraZeneca, Basilea, Cubist, FAB Pharma, Gilead, InfectoPharm, MSD, Novartis, Pfizer, Roche Pharma, Tetraphase and The Medicines Company. SM-P reports acting as a speaker for Ecolab, and as a consultant for Clorox and Xenex. DLP has received research grants from AstraZeneca and has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from Cubist Pharmaceuticals, Merck, AstraZeneca, SanofiAventis, Pfizer, Johnson & Johnson and Leo Pharmaceuticals. AYP has attended an advisory board meeting for Merck with no honorarium. KSK serves as a consultant for Achaogen, Merck, Pfizer and the Medicines Company, and

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Table 1: Summary of the Delphi process

Round	Themes / Questions	Participants
1	• Determination of appropriate questions to be included in the process	19
2	• Whether different endpoints required for GN / GP BSI • Whether different endpoints required for early phase / late phase trials • Whether patient-centred or clinical / microbiological outcomes should be preferred as a primary endpoint	24
3	• Agreement sought on requirement for different GN / GP endpoints • Agreement sought on requirement for different early phase / late phase endpoints • Strengths and weaknesses of endpoints used in previous trials discussed with specific examples • Timing of endpoint determination discussed • Utility of laboratory values (e.g. CRP, Procalcitonin, WCC), clinical variables (e.g. fever, symptom resolution) and microbiological tests (e.g. blood cultures) in endpoints discussed • Use of other quality of life measures in endpoints	17
4	• Agreement sought on whether protocol violations should be avoided as part of primary endpoints • Agreement sought on whether mortality attributable to BSI should be avoided for use in endpoints in preference to all-cause mortality • Agreement sought on best specific measures to include in primary and secondary endpoints, including the potential role for surrogate markers • Voting on proposed endpoints definitions with comments sought	19
5	• Voting on consensus definitions for primary and secondary endpoints in therapeutic trials for BSI caused by *S. aureus* and GN organisms	18
6	• Voting on applicability of a desirability of outcome ranking (DOOR) score for BSI	19

GN = Gram negative, GP = Gram positive, BSI = Bloodstream infection, CRP = C-reactive protein, WCC = white cell count

Table 2: Endpoints used in RCTs and prospective observational studies of BSI published Jan 2005 – Apr 2016 [5, 21, 22, 32-51]

Category	Specific End Point[a]	Number of studies using each endpoint		
		Primary	Secondary	Combined frequency of endpoint
Objective clinical outcome				
	Mortality			
	In-hospital mortality	3	2	5
	7 days	1	0	1
	14 days	4	1	5
	21 days	1	0	1
	28 days	3	1	4
	30 days	3	0	3
	42 days	0	1	1
	60 days	1	0	1
	90 days	4	3	7
	12 weeks	1	0	1
Clinical outcome other than mortality				
	ICU free days at 28 days	1	0	1
	Duration of fever	0	4	4
	Duration of antibiotic therapy	1	3	4
	Organ failure free days	0	1	1
	Clinical cure/response to treatment	7	6	13
	Length of hospital stay post BSI	0	2	2
	Development of antibiotic resistance	0	3	3
Subjective clinical measures				
	Measures of functional status/ QOL indicators	0	2	2
	Attributable mortality	1	2	3
Microbiological outcome				
	Bacteriological cure (*Incorporating clearance of blood cultures*)	5	10	15
	Clostridium difficile diarrhoea	0	4	4
Surrogate endpoints				
	Decrease in CRP	0	1	1
	Procalcitonin level	0	1	1
	Markers of severity of inflammation	0	1	1
	Resolution of inflammatory response	1	3	4
Cost		0	2	2
Safety		1	11	12

[a] When not specifically defined we inferred primary and secondary endpoints

Table 3: Consensus definitions for BSI studies

***Staphylococcus aureus* BSI**	**Gram-negative BSI (including organisms associated with >10% mortality, e.g. *E. coli*)**
Pilot trial to select an intervention for a larger definitive trial	
Primary outcome: Success is defined by all of the following criteria being met at 7 days after randomization: 1. Patient alive 2. Fever resolved 3. Stable or improved SOFA[a] score (compared to baseline) 4. Blood cultures negative for *S. aureus* *In addition:* No isolation of *S. aureus* in blood cultures or another sterile site from 8 to 90 days after randomisation	*Primary outcome*: Success would be defined at 7 days from randomization by all of the following: 1. Patient alive 2. Fever resolved 3. Symptoms attributed to the focus of infection have resolved 4. SOFA[a] score stable or improved 5. Negative blood cultures in days 3-7 post randomisation[b]
Definitive antibiotic trial, in a pragmatic 300+ patient investigator-initiated study, the purpose of which is to influence clinical practice	
Primary outcome: Success of therapy is defined at 90 days by presence of all of the following: 1. Patient alive 2. No evidence of microbiologically confirmed treatment failure, defined as either: (a) Persistence of *S. aureus* BSI more than 7 days (b) Isolation of *S. aureus* from a sterile site (blood, joint fluid, tissue) more than 14 days from randomisation	*Primary outcome*: Patient alive at 90 days after randomization *Composite secondary outcome*: Success would be defined at 7 days from randomization by all of the following: 1. Patient alive 2. Fever resolved 3. Symptoms attributed to the focus of infection have resolved 4. SOFA[a] score stable or improved 5. Negative blood cultures in days 3-7 post randomisation[b]

a. can use modified SOFA if outside ICU
b. taken only if the patient is febrile >=38°C, to prevent unnecessary additional protocol-driven blood collection

Table 4. Advantages and disadvantages of different primary endpoints for studies of antibiotics in treatment of BSI.

End Point	Advantages	Disadvantages
1. Objective clinical outcomes		
All-cause mortality	Hard clinical outcome, highly objective, important to patients, accurate and simple to collect	Large sample size generally required to demonstrate difference Contentious as to ideal time of collection which leads to heterogeneity in end points Fails to assess other patient centred end points such as improvements in quality of life
2. Subjective clinical outcomes		
Attributable mortality	Highly relevant in elderly population and patients with multiple co morbidities	Limited objectivity as open to interpretation, and mortality cannot reliably be attributed to BSI in isolation
Quality of life / Functional Status	Patient centred outcome	Lack of standardisation may lead to outcome measures which are not reproducible, requires measurement at baseline, requires consensus in the application of robust standardised measures. May require administration of complex questionnaires.
Resolution of symptoms	In combination with clinical signs provides the end point of clinical cure - may require smaller sample size to demonstrate differences in efficacy, forms part of daily clinical practice	Interpretation of symptoms remains a subjective measure, may not be suitable as an endpoint in isolation
3. Microbiological outcomes		
Clearance of the pathogen of interest	Objective measure, highly relevant for *S. aureus* and some Gram-negative organisms, simple to assess	Not relevant for all pathogens, requires timely recollection of blood cultures
Clostridium difficile diarrhoea	Objective measure	Large sample size to demonstrate difference; variation in laboratory testing methodology
Colonisation with multi-resistant organisms	Objective measure	Requires additional sampling, variable laboratory methods and test sensitivity
Microbiome / resistome effects	Objective measure of 'collateral damage' from antibiotics	Limited experience in the use of metagenomic data as an outcome variable in clinical trials; unclear which measures best compare outcomes between treatment groups
4. Surrogate endpoints		
Biomarkers	Improve power and/or practicality of trial	Must be demonstrated to be a suitable substitute for clinically meaningful end point No reliable or well-validated surrogate endpoint for mortality currently exists for mortality in BSI
Systemic inflammatory response syndrome	Measured as part of daily clinical practice. Smaller sample sizes to demonstrate efficacy. Easily collected	Response of these variables or lack of response may not be attributable to antibiotic alone; have never been validated in this context

5. Composite endpoints		
Combined	Improve power of study	May be difficult to interpret if endpoints demonstrate co-linearity
Propensity Score / Ranked	Improve power of the study, outcomes; may be graded	Complex statistical analysis, clinicians less familiar with interpretation
6. Desirability of outcome ranking (DOOR) score		
	Potential to provide a unified scale for all bloodstream studies and different pathogens	Complexity of assigning and implement a scale with correctly weighted ranks Complexity of analysis
	Capacity to improve the power of the study to detect superiority of treatment rather than non-inferiority	May obscure non-inferiority or introduce bias. Difficulty in achieving consensus on components of the DOOR scale

Table 5 Differences between endpoint requirements for drug registration studies and pragmatic investigator-initiated trials

Endpoint requirements for drug registration	**Endpoint requirements for pragmatic investigator-initiated trials**
Primary endpoint often involves clinical and microbiological response at an early stage (e.g. resolution of symptoms with microbiological clearance)	Primary endpoint needs to reflect patient-centered outcomes
Secondary endpoints often involve primary outcome measures assessed at a delayed time period (e.g. 28 days)	Secondary endpoints often assess a range of other clinical outcomes, may be pathogen specific (e.g. *S. aureus*)
May involve more laboratory testing (e.g. microbiological test of cure) as part of endpoints	Often aim to keep additional laboratory testing to a minimum to curb costs and limit any patient burden beyond normal clinical care
Purpose of the study is to assess efficacy and safety to enable registration of the product for market	Purpose of the study is to optimise existing therapeutic strategies and inform clinical practice
Study targets regulatory bodies (e.g FDA, EMA)	Study targets clinicians